THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Drolet M, Bénard É, Boily M-C, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2015; published online March 3. http://dx.doi.org/10.1016/S1473-3099(14)71073-4.

Supplementary appendix

Table S1. Description of HPV vaccination programs and vaccination coverage for each study country/region

Country	Vaccine used	Financing	Availability of vaccine / Program start	Program description[*]	3 doses Vaccination coverage (year)[†]
Australia	Quadrivalent	Public	April 2007	School-based program: • Girls 12-13 yrs • Boys 12-13 yrs since February 2013 School-based catch-up: • Girls 14-17 yrs (2007-2009) • Boys 14-15 yrs (2013-2014)	School-based program: • Girls 12-13 yrs: 71% (2012) • Boys 12-13: NA School-based catch-up: • Girls 14-17 yrs:70% (2012) • Boys 14-15 yrs: NA
			July 2007	GP/Community catch-up: • Women 18-26 yrs (2007-2009)	GP/Community catch-up: • Women 18-19 yrs: 69% (2012) • Women 20-26 yrs: 44% (2012)[‡]
Canada (Manitoba)	Quadrivalent	Private	August 2006 (vaccine available privately)	Private vaccination: • Girls/women 9-26 yrs	Private vaccination: • Girls/women 9-26 yrs: 3% at least one dose (2009)
		Public	September 2008	School-based program: • Girls Grade 6 (≈ 11-12 yrs)	School-based program: Girls 11-12 yrs : about 50% (2009)
Denmark	Quadrivalent	Private	October 2006	Private vaccination: • Girls and boys ≥ 9 yrs	Private vaccination: • No information for total group of females. About 15% for those born in 1985-1992
		Public	January 2009	GP Childhood vaccination program: • Girls 12 yrs	Children vaccination program by GPs: • Girls 12 yrs: 79% (2012)
			October 2008	GP Catch-up girls: • Girls 13-15 yrs (2008-2010)	Catch-up: • Girls 13-15 yrs: 81% (2012)
			August 2012	GP Catch-up women: • Women 20-27 yrs (2012-2013)	GP Catch-up women: Women 20-27 yrs: 2% (2012)[§]
Germany	Quadrivalent and Bivalent (Quadrivalent: 90% of doses)	Public	March 2007	GP/community program • Routine vaccination of girls 12-17 yrs	Girls 16-18: about 40% (2009)
New Zealand	Quadrivalent	Public	September 2008	School-based/GP/community program: • Girls 11-12 yrs; School-based/GP/community catch-up: • Girls 13-20 yrs (2008-2010)	School-based/GP/community program: • Girls 11-12 yrs: around 55% (2012) (57% in Auckland) School-based/GP/community catch-up: Girls 13-20 yrs (2008-2010): 50% (2012)

Country	Vaccine used	Financing	Availability of vaccine / Program start	Program description[*]	3 doses Vaccination coverage (year)[†]
Sweden	Quadrivalent	Partially subsidized	October 2006 (Opportunistic vaccination)	Opportunistic vaccination: • Girls 13-20	25% at least one dose (2011) Leval 2013
		Public	2012	School-based program: • Girls 11-12 yrs; School-based catch-up: Girls 13-18 yrs	NA NA
UK - England	Bivalent, switch to Quadrivalent in September 2012	Public	September 2008	School-based program: • Girls 12-13 yrs School-based/GP catch-up: • Girls 14-17 yrs	School-based program: • Girls 12-13 yrs: 84% (2011) Catch-up: • Girls 14-17 yrs: 56% (range from 39 to 76%) (2011)
UK- Scotland	Bivalent, switch to Quadrivalent in September 2012	Public	September 2008	School-based program: • Girls 12-13 yrs School-based/GP catch-up: • Girls 14-17 yrs	School-based program: • Girls 12-13 yrs: 90% (2011) Catch-up (in and out of school): • Girls 13-17 yrs: 88% (33% among school leavers) (2011)
US	Quadrivalent and Bivalent (mostly Quadrivalent)	Mix of public and private	June 2006	Primary care providers vaccination: • Girls/women 11-12 yrs routine and 13-26 yrs, if not previously vaccinated • Boys/men 11-12 yrs routine and 13-21 yrs if not previously vaccinated since October 2011 • MSM 22-26 yrs or immunocompromised since October 2011	Routine and catch-up vaccination: • Girls 13-17 yrs: 33% (2012) • Women 19-26 yrs: 21% at least one dose (2010)

[*] The predominant delivery method is stated where mixed methods were allowed

[†] 3-dose coverage reported, but if unavailable, coverage for at least one dose is indicated

[‡] Possible underreporting of HPV vaccination coverage for women 20-26 years old as reported in Brotherton et al. Vaccine 2014

[§] Few women have received 3 doses of the vaccine at this time since the catch-up program was not initiated before 2012 (37-50% had received the first HPV vaccine, and 28-39% had received the second)

Data sources for vaccination coverage and program descriptions:

Australia

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3. Personal communication with Julia Brotherton
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Canada

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Denmark

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2. Baandrup L, Blomberg M, Dehlendorff C, Sand C, Andersen KK, Kjaer SK. Significant decrease in the incidence of genital warts in young Danish women after implementation of a national human papillomavirus vaccination program. *Sex Transm Dis* 2013; **40**(2): 130-5.
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5. Personnal communication with Louise Baandrup

Germany

1. Mikolajczyk RT, Kraut AA, Horn J, Schulze-Rath R, Garbe E. Changes in incidence of anogenital warts diagnoses after the introduction of human papillomavirus vaccination in Germany-an ecologic study. *Sex Transm Dis* 2013; **40**(1): 28-31.

New Zealand

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2. Oliphant J, Perkins N. Impact of the human papillomavirus (HPV) vaccine on genital wart diagnoses at Auckland Sexual Health Services. *The New Zealand medical journal* 2011; **124**(1339): 51-8.

Sweden

1. Leval A, Herweijer E, Arnheim-Dahlstrom L, et al. Incidence of genital warts in sweden before and after quadrivalent human papillomavirus vaccine availability. *J Infect Dis* 2012; **206**(6): 860-6.

UK (England)

1. Mesher D, Soldan K, Howell-Jones R, et al. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunisation in England. *Vaccine* 2013; **32**(1): 26-32.
2. Department of Health. Annual HPV vaccine coverage in England201/2011. http://media.dh.gov.uk/network/211/files/2012/03/120319_HPV_UptakeReport2010-11-revised_acc.pdf (accessed April 2014).

UK (Scotland)

1. Kavanagh K, Pollock KG, Potts A, et al. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. *Br J Cancer* 2014; **110**(11): 2804-11.
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US

1. Centers for Disease Control and Prevention. Adult Vaccination Coverage — United States, 2010. MMWR 2012;61:66- 72;
2. Centers for Disease Control and Prevention. Human Papillomavirus Vaccination Coverage Among Adolescent Girls, 2007–2012, and Postlicensure Vaccine Safety Monitoring, 2006–2013 — United States. MMWR 2013;62:591-595.

Table S2. Methodological quality and risk of bias in studies examining changes in HPV infection between the pre- and post-vaccination periods.

Authors	Cummings 2012	Kahn 2012	Tabrizi 2012	Markowitz 2013	Mesher 2013	Sonnenberg 2013	Kavanagh 2014
Study design	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis
Country	United States	United States	Australia	United States	England	Britain	Scotland
Funding	National Institutes of Health	National Institutes of Health	Australian National Health and Medical Research Council, and Anti-Cancer Council for Victoria	Centers for Disease Control and Prevention	Public Health England	UK Medical Research Council, Wellcome Trust, Economic and Social Research Council and the Department of Health	Scottish government, Chief Scientist Office
Risk of selection bias							
Subjects included in the study	Clinic-based: Women attending 1 of 3 urban primary care clinics in Indianapolis	Clinic-based: Young women attending 2 primary care clinics in Cincinnati who had had sexual contact. Great proportion of minority and low-income women	Clinic-based: Women recruited from participating family planning clinics for Pap screening in Sydney, Melbourne, and Perth	Population-based: Participants in NHANES which is designed to be nationally representative of the civilian, non-institutionalized US population	Clinic-based: Women undergoing chlamydia screening at community sexual health services, general practice and youth clinics in 7 regions around England	Population-based: Participants in NATSAL which is designed to be nationally representative of the British population	Population based: Women attending their cervical screening appointment across Scotland
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Low Unlikely changes in the clientele of primary care clinics between the pre- and post-vaccination periods	Low Unlikely changes in the clientele of primary care clinics between the pre- and post-vaccination periods	Low Unlikely changes in the clientele of family planning clinics between the pre- and post-vaccination periods	Low Unlikely changes in the NHANES participants between the pre- and post-vaccination periods	Medium Documented changes in the clientele receiving chlamydia testing between the pre- and post-vaccination periods	Medium Possible changes in the NATSAL participants between the pre- and post-vaccination periods (> 10 yrs between the 2 periods). Both surveys are weighted to Census data from the time.	Low No documented changes in screening rates of women aged 20-24 years old between the pre- and post-vaccination periods
Risk of information bias							
HPV testing	PCR Roche Linear Array test which detects 37 different HPV types	PCR Roche Linear Array test which detects 37 different HPV types	Amplicor HPV test kit (Roche Molecular system) (13 HPV types) and PGMY09-PGMY11 PCR-ELISA Roche Linear Array HPV Genotyping test	PCR Roche Linear Array test which detects 37 different HPV types	2008: Hybrid Capture 2 and Roche Linear Array 2010-2012: HPV+ In-house multiplex PCR and Luminex-based genotyping test (13 HPV types)	In-house Luminex-based genotyping assay (20 HPV types) in urine samples	Multimetrix HPV Assay which detects 18 high-risk types
Performance of the HPV test used	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported
Outcome used in publication	Odds ratios of HPV prevalence (crude)	HPV prevalence difference (adjusted)	Odds ratios of HPV prevalence (adjusted)	HPV prevalence ratio (crude)	Odds ratios of HPV prevalence (adjusted)	Odds ratios of HPV prevalence (adjusted)	HPV prevalence over time
Potential for information bias: Errors in the identification of HPV+ during the pre and post-vaccination period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium/High Potential for masking by HPV16/18, particularly in the pre-vaccine period; different tests used in the pre- and post-vaccination periods Which may have contributed to higher prevalence of non-vaccine types in the post-vaccination period	High Potential for masking by HPV16/18, particularly in the pre-vaccine period; Urine is a suboptimum specimen for the detection of HPV; Differences in methods of sample collection, preparation and storage between the pre- and post-vaccination periods	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period
Risk of confounding							
Potential confounders considered	Analysis matched on age at enrollment, clinic site and reported sexual activity (yes, never) at time of enrollment	Analysis adjusted for demographic characteristics (race, health insurance plan…), gynecologic history (number of times pregnant, history of Chlamydia, AGW), behaviors (age at first sexual intercourse, number male sexual partners, condom use, smoking…) using propensity scores	Analysis adjusted for age, contraceptive use, region, socioeconomic group and smoking status (these variables differed significantly between the 3 groups of women)	Analysis adjusted for race/ethnicity, lifetime number of sex partners for girls aged 14-19 years old. No adjustment for the other age groups, but all analysis weighted to represent the U.S population	Analysis adjusted for sexual history, age, venue type, ethnicity and chlamydia positivity	No adjustment in the comparison of HPV prevalence between the pre- and post-vaccination periods, but all analysis weighted to represent the British population	No adjustment in the analysis of changes of HPV prevalence over time
Potential for confounding: Changes in HPV infection between the pre and post-vaccination periods could be diluted/exacerbated by other variables	Medium Few risk factors considered and residual confounding by other factors associated with HPV vaccination and infection is possible (e.g., changes in sexual activity)	Low/Medium Several risk factors were considered. However, residual confounding by other factors associated with HPV vaccination and infection may still be present	Medium Few sexual behavior factors considered and residual confounding by other factors associated with HPV vaccination and infection is possible (e.g., changes in sexual activity)	Low/Medium Few factors considered for girls aged 14-19 years old, but weighted analysis	Medium Several risk factors were considered. However, residual confounding by other factors associated with HPV vaccination and infection can still be present (e.g., changes in sexual activity)	Medium/High No adjusted analysis of changes in HPV prevalence over time and likely changes over a 10-year period in factors associated with HPV vaccination and infection (e.g., changes in sexual activity documented when comparing NATSAL-2 and -3 [1])	Medium No adjusted analysis of changes in HPV prevalence over time. Confounding by factors associated with HPV vaccination and infection may be present (e.g., changes in sexual activity)

Authors	Cummings 2012	Kahn 2012	Tabrizi 2012	Markowitz 2013	Mesher 2013	Sonnenberg 2013	Kavanagh 2014
Study design	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis
Country	United States	United States	Australia	United States	England	Britain	Scotland
External validity							
External validity: Results can be generalized to the population at the country/region level	Medium Young women attending to urban primary care clinics may not represent the overall population (e.g., different vaccination coverage)	Low/Medium Women attending to the 2 primary care clinics may not be representative of the overall population (e.g., different vaccination coverage). Minorities and women from low socio-economic status are overrepresented	Medium Young women attending family planning clinics may not represent the overall population (e.g., different vaccination coverage)	Medium/High The survey was designed to be representative of the general population but non-participants could still be different than participants with respect to variables not considered in the sampling design.	Medium Chlamydia screening recommended for all sexually-active young women and uptake was 40% in 2011. However, women undergoing chlamydia screening may not be representative of the overall population (e.g., different vaccination coverage)	Medium/High The survey was designed to be representative of the general population. However, participants and those providing urine samples might not be fully representative of the general population, despite efforts to adjust for known biases and the use of additional weights for urine selection and urine non-response.	Medium Women participating in screening may not represent to overall population (e.g., different vaccination coverage)

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Table S3. Methodological quality and risk of bias in studies examining changes in anogenital warts between the pre- and post-vaccination periods.

Authors	Oliphant 2011	Bauer 2012	Kliewer 2012	Leval 2012	Ali 2013	Baandrup 2013	Howell-Jones 2013	Flagg 2013	Mikolajczyk 2013	Nsouli-Maktabi 2013	Sandø 2013
Study design	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends
Country	New Zealand	United States	Canada	Sweden	Australia	Denmark	England	United States	Germany	United States	Denmark
Funding	No funding required	CDC, California Department of Public Health	Department of Health of Manitoba	National Research School in Health Care Sciences, Strategic Research Program (Karolinska Institutet), Erasmus Programme	CSL Biotherapies	Aragon Foundation, Aase and Ejnar Danielsen Foundation, Mermaid II Project	Public Health England	Centers for Disease Control and Prevention	Sanofi-Pasteur MSD	Not mentioned	Not mentioned
Risk of selection bias											
Subjects included in the study	Clinic-based: New clients of 1 sexual health service in Auckland	Health provider/insurance-based: Clients of the California Family Planning access care & treatment (FPACT) program	Population-based: Manitoba population from the population registry	Population-based: Sweden population from Statistics Sweden	Clinic-based: New clients of 8 sexual health services across Australia (Australian born)	Population-based: Denmark population from Statistics Denmark	Health provider/ based : Women diagnosed at Genitourinary medicines (GUM) and England population from national statistics as denominator;	Health provider/insurance-based : Enrollees in approximately 100 private health insurance plans across US	Health provider/insurance-based : Enrollees in 1 large health insurance company across Germany	Health provider/insurance-based : All individuals who served in the US Armed Forces	Population-based: Denmark population from Statistics Denmark
Potential for of selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Medium/High Possible changes in the clientele of the sexual health service as reflected by an increasing annual number of clients in the post-vaccination period	Low Unlikely change in the FPACT (family planning program for low-income individuals) clientele between the pre- and post-vaccination periods	Low Entire population of Manitoba	Low Entire population of Sweden	Medium/High Possible changes in the clientele of the sexual health services in the pre- and post-vaccination periods as reflected by increasing annual number of clients and % of clients with chlamydia after 2006	Low Entire population of Denmark	Low/Medium Possible changes in GUM services clientele in the pre- and post-vaccination periods	Low Unlikely change in enrollees of insurance plans between the pre and post-vaccination periods. No decrease in Pap test or pelvic examination (opportunities to diagnose AGW) over time	Low Unlikely change in enrollees of insurance plans between the pre- and post-vaccination periods	Low Unlikely change in the Armed Forces population between the pre- and post-vaccination periods	Low Entire population of Denmark
Risk of information bias											
Data source	Medical records (available in the sexual health clinic database)	FPACT database (clinical encounter claims data)	Manitoba medical claims and hospital discharges	National patient register, Prescribed drug register	Medical records	National patient register	Genitourinary Medicine Clinic Activity Dataset (GUMCAD) (diagnoses at GUM clinics nationally	Truven Health Analytics MarketScan Commercial Claims and Encounters Database	German Pharmaco-epidemiological research database	Defense Medical Surveillance System	National patient register, Medical Products Statistics Register
Anogenital wart case definition	Clinical diagnosis	ICD-9 codes 078.10, 078.11 OR prescription of Imiquimod or Podophyllotoxin	Treatments (1 of 14 tariff codes for AGW treatments) OR hospitalization for AGW with ICD-9 code 078.11 OR 078.1, 078.10, 078.19 and related procedure OR ICD-10 A630 OR B07 and related procedure)	ICD-10 code A63 OR prescription of Imiquimod or Podophyllotoxin	Clinical diagnosis	ICD-10 code A63.0	Clinical diagnosis	1) ICD-9 codes 078.11 OR 2) ICD-9 code 078.1, 078.10, 078.19 <u>and</u> therapeutic procedure or diagnosis of benign anogenital neoplasm OR 3) ≥ 1 prescription for AGW treatment <u>and</u> therapeutic procedure or diagnosis of benign anogenital neoplasm	ICD-10 code A63.0	ICD-9 code 078.1	ICD-10 code A63.0, OR prescription of Podophyllotoxin
Outcome used	Annual proportion of new clients diagnosed with AGW	Annual proportion of FPACT clients diagnosed with AGW	Annual incidence rate of diagnosed AGW in the population	Annual incidence rate of diagnosed AGW in the population	Annual proportion of new clients with diagnosed AGW	Annual incidence rate of diagnosed AGW in the population	Annual incidence rate of GUM-diagnosed AGW in the population	Annual proportion of insured individuals with diagnosed AGW	Annual incidence rate of diagnosed AGW among insured individuals	Annual incidence rate of diagnosed AGW among US Forces members	Annual proportion of the population with diagnosed AGW
Numerator	Number of newly diagnosed AGW cases between Jan 2007 – June 2010	Number of first ever cases diagnosed after 2007 (cases prior to 2007 excluded) per year	Number of newly diagnosed AGW case each year (washout period of 12 months)	Number of newly diagnosed AGW cases each year, (washout period of 6 months)	Number of newly diagnosed AGW cases per year	Number of newly diagnosed AGW cases each year (washout period of 12 months)	Number of first diagnosed AGW cases since 2006, each year	Number of patients with AGW diagnosis each year	Number of newly diagnosed case each year, (washout period of 12 months)	Number of first ever diagnosed AGW case	Number of AGW cases each year

Authors	Oliphant 2011	Bauer 2012	Kliewer 2012	Leval 2012	Ali 2013	Baandrup 2013	Howell-Jones 2013	Flagg 2013	Mikolajczyk 2013	Nsouli-Maktabi 2013	Sandø 2013
Study design	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends
Country	New Zealand	United States	Canada	Sweden	Australia	Denmark	England	United States	Germany	United States	Denmark
Denominator	Total number of new patients per year	All clients registered in the FPACT each year	Annual population estimates	Annual population estimates	Total number of new patients per year	Annual population estimates	Annual population estimates	Total number of clients enrolled in in health insurance plans each year	Total number of clients of 1 large insurance company each year	Total number of individuals who served in the US Forces each year	Annual population estimates
Potential for information bias: Errors in the identification of diagnosed AGW cases during the pre and post-vaccination period	Low AGW are directly diagnosed by physicians	Medium Sensitivity/specif-icity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium Sensitivity/speci-ficity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium Sensitivity/specifi-city of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Low AGW are directly diagnosed by physicians	Medium Sensitivity/speci-ficity of algorithm to correctly identify diagnosed AGW not specified and AGW treated by GP not included, unlikely to change over time unless awareness is associated with likelihood of including code	Low AGW are directly diagnosed by physicians in GUM clinics,	Medium Sensitivity/speci-ficity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium Sensitivity/speci-ficity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium Sensitivity/speci-ficity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium Sensitivity/specificity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code
Risk of confounding											
Potential confounders considered	Analysis stratified by age and gender	Analysis stratified by age and gender	Analysis stratified by age and gender	Analysis stratified by age and gender	Analysis stratified by age, gender, sexual orientation and residential status	Analysis stratified by age and gender	Analysis stratified by age and gender, and adjusted for chlamydia diagnoses and area	Analysis stratified by age, gender, region, and insurance plan type	Analysis stratified by age and gender	Analysis stratified by age and gender	Analysis stratified by age and gender
Potential for confounding: Changes in diagnosed AGW between pre and post-vaccination periods could be diluted/exacerba-ted by other variables	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity); data suggesting increasing sexual activity over time in Sweden	High Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour); data suggest increasing proportion of clients with chlamydia after 2007	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour); data suggesting increases in diagnosis of all STIs	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)
External validity											
External validity: Results can be generalized to the population at the country/region level	Medium Clients of 1 sexual health clinic may not represent the overall population (e.g., different vaccination coverage)	Medium FPACT is a program for low-income individuals and 87% of participants are females. Results could be different for medium/high-income individuals (e.g., different vaccination coverage)	High Entire population	High Entire population	Medium Clients of 8 sexual health clinics possibly representative of sexual health clinic clients in Australia, may not represent the overall population (e.g., different vaccination coverage)	Medium/High Entire population Contains all cases of AGW admitted to hospital or in outpatient clinics	Medium/High About 95% of AGW diagnoses are made in GUM clinics (~85% sample of national data used)	Medium/High The Truven Health Analytics contains data from 100 health insurance plan throughout the US (n=13 million in 2010). Results could be different for uninsured individuals	Medium/High The insurance plan includes > 6million individuals, 8% of the German population and is demographically representative. Results could be different in uninsured individuals	Medium/High All members of the Armed Forces are included, but results could be different for individuals not in the Armed Forces	High Entire population

CDC: Centers for Disease Control and Prevention

Table S4. Methodological quality and risk of bias in studies examining changes in high-grade lesions between the pre- and post-vaccination periods.

Authors	Brotherton 2011/AIHW 2013	Niccolai 2013
Study design	Time-trend analysis	Time-trend analysis
Country	Australia	United States
Funding	none	Centers for Disease Control and Prevention
Risk of selection bias		
Subjects included in analysis	Population-based: Women included in the Victorian Cervical Cytology Registry	Population-based: Statewide surveillance registry in Connecticut
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Medium Possible changes in participants to cervical cancer screening between the pre- and post-vaccination periods	Medium Possible changes in participants to cervical cancer screening between the pre- and post-vaccination periods
Risk of information bias		
Diagnosis of cervical lesions	The registry receives data from almost all cytology and cervical histopathology taken in Australia	The surveillance system receives data from all 34 pathology laboratories in Connecticut
Outcome used	Annual incidence of high grade lesions	Annual incidence of high grade lesions
Potential for information bias: Errors in the identification of pre-cancerous cervical lesions during the pre and post-vaccination period	Medium Sensitivity/specificity may change after vaccination, but unlikely to change during the first years of the vaccination program.	Medium Sensitivity/specificity may change after vaccination, but unlikely to change during the first years of the vaccination program.
Risk of confounding		
Potential confounders considered	Analysis stratified by age	Analysis stratified by age, area-based measures of ethnicity and race, and county type (urban-rural)
Potential for confounding: Changes in precancerous between pre and post-vaccination periods could be diluted/exacerbated by other variables	Medium/High Other factors could potentially cause changes in the incidence of precancerous cervical lesions (e.g., changes in screening guidelines, sexual activity). Changes in screening guidelines documented in 2006[1].	Medium/High Other factors could potentially cause changes in the incidence of precancerous cervical lesions (e.g., changes in screening guidelines, sexual activity). Changes in screening guidelines and in screening among women documented in the US[2].
External validity		
Results can be generalized to the population at the country/region level	Medium/High Women participating in screening may not be representative of the overall population (e.g., different vaccination coverage)	Medium/High Women participating in screening may not be representative of the overall population (e.g., different vaccination coverage)

AIHW: Australian Institute of Health and Welfare

References:

1. NHMRC. Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities, 2005. http://www.nhmrc.gov.au/publications/synopses/wh39syn.htm (accessed Dec 2010).

2. MMWR Jan 2013. Cervical cancer screening among women aged 18-30 years – United States, 2000-2010

Table S5. Pre and post-vaccination years considered in the meta-analysis.

Study	Country	HPV vaccination introduction	Pre-vaccination years considered in the meta-analysis	Post-vaccination years [ǁ]				
				1	2	3	4	5 [§]
HPV infection [*]								
Cummings 2012	U.S.	2006	1995-2005				2010	
Kahn 2012 [‡]	U.S.	2006	2006-2007			2009	2010	
Tabrizi 2012	Australia	2007	2005-2007			2010	2011	
Markowitz 2013	U.S.	2006	2003-2006	2007	2008	2009	2010	
Mesher 2013	England	2008	2008		2010	2011	2012	
Sonnenberg 2013	Britain	2008	1999-2001		2010	2011	2012	
Kavanagh 2014 [‡]	Scotland	2008	2009-2010			2011	2012	
AGW consultations [†]								
Oliphant 2011	New Zealand	2008	2007-2008	2009	2010			
Bauer 2012 [‡]	U.S.	2006	2007		2008	2009	2010	
Kliewer 2012	Canada	2008	2006-2008	2009				
Leval 2012	Sweden	2006	2006	2007	2008	2009	2010	
Ali 2013	Australia	2007	2005-2007	2008	2009	2010	2011	2012
Baandrup 2013	Denmark	2009	2007-2009	2010	2011			
Howell-Jones 2013	England	2008	2006-2008	2009	2010	2011		
Flagg 2013	U.S.	2006	2004-2006	2007	2008	2009	2010	
Mikolajczyk 2013	Germany	2007	2005-2007	2008				
Nsouli-Maktabi 2013	U.S.	2006	2004-2006	2007	2008	2009	2010	2011
Sandø 2013	Denmark	2009	2007-2009	2010	2011			
High–grade precancerous lesions								
Brotherton 2011/AIHW 2013	Australia	2007	2005-2007	2008	2009	2010	2011	
Niccolai 2013 [‡]	U.S.	2006	2008			2009	2010	2011

AIHW: Australian Institute of Health and Welfare

[*] For HPV infection, pre- and post-vaccination years were determined in original studies. The impact measure presented in original studies compared the combined post-vaccination years to the combined pre-vaccination. The only exception is the study by Kavanagh et al., in which yearly prevalence was presented separately for 2009,

2010, 2011, and 2012. We considered 2009 and 2010 as pre-vaccination years since the vaccination coverage was very low and 2011 and 2012 as post-vaccination years.

† For anogenital warts, pre-vaccination years (up to 3 according to the data available) were determined for the purpose of the meta-analysis. We included the calendar year of HPV vaccination introduction in the pre-vaccination period because year-end vaccination coverage with more than one dose was very low. All subsequent years were considered as post-vaccination years.

‡ Studies where the pre-vaccination years considered in the analysis included 1 or 2 years after the introduction of HPV vaccination, but during which the vaccination coverage was considered low (i.e. < 15%).

§ Since only two studies examined AGW during the fifth year after the introduction of HPV vaccination (1 with a high coverage and 1 with a low coverage), we restricted the analysis to four years. Similarly, for cervical lesions, the analysis was restricted to the first four years.

‖ Blanks in the post-vaccination years indicate that the study did not evaluate the outcome in this year

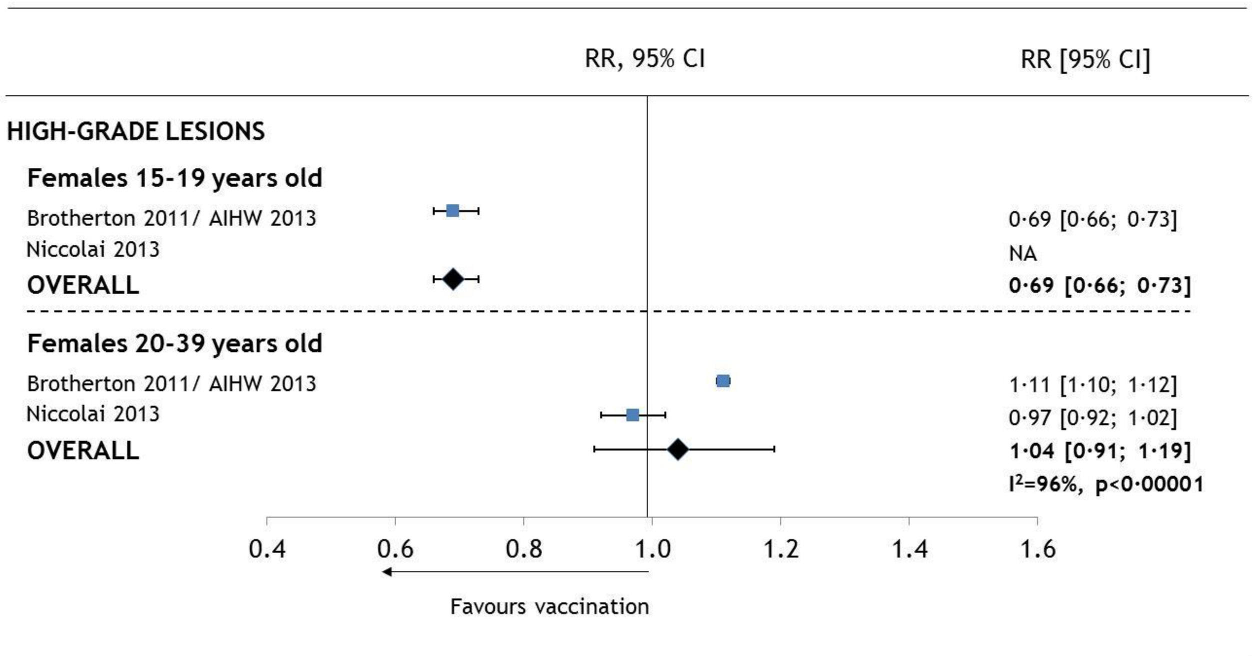
Table S6. Results of the sensitivity analysis using the results of Sandø et al instead of Baandrup et al.

	Baandrup et al.				Sandø et al.			
	Females		Males		Females		Males	
	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs
Results presented in Figure 3								
Study estimate	0·54 (0·49;0·60)	0·79 (0·74;0·83)	0·80 (0·63;1·01)	0·82 (0·77;0·87)	0·48 (0·46;0·51)	0·97 (0·95;0·99)	0·67 (0·63;0·72)	1·09 (1·07;1·12)
Summary for the quadrivalent vaccine	0·69 (0·60;0·79)	0·89 (0·79;1·02)	0·95 (0·84;1·08)	1·01 (0·88;1·17)	0·67 (0·56;0·80)	0·92 (0·82;1·03)	0·91 (0·78;1·07)	1·05 (0·93;1·18)
Heterogeneity for the quadrivalent summary estimate	I^2 = 97% p<0·00001	I^2 = 99% p<0·00001	I^2 = 93% p<0·00001	I^2 = 99% p<0·00001	I^2 = 99% p<0·00001	I^2 = 99% p<0·00001	I^2 = 96% p<0·00001	I^2 = 99% p<0·00001
Results presented in Figure S2- Appendix								
Vaccine								
Quadrivalent	0·69 (0·60;0·79)	0·89 (0·79;1·02)	0·95 (0·84;1·08)	1·01 (0·88;1·17)	0·67 (0·56;0·80)	0·92 (0·82;1·03)	0·91 (0·78;1·07)	1·05 (0·93;1·18)
Bivalent	0·96 (0·94;0·97)	1·00 (0·98;1·01)	1·03 (1·01;1·05)	1·02 (1·00;1·03)	0·96 (0·94;0·97)	1·00 (0·98;1·01)	1·03 (1·01;1·05)	1·02 (1·00;1·03)
	I^2 = 95% p<0·00001	I^2 = 62% p=0·10	I^2 = 26% P=0·25	I^2 = 0% p=0·96	I^2 = 93% p=0·0001	I^2 = 50% p=0·16	I^2 = 53% p=0·15	I^2 = 0% ·p=0·65
Quadrivalent vaccine								
Coverage								
Low	0·86 (0·79;0·94)	1·02 (0·90;1·16)	1·07 (0·93;1·22)	1·13 (0·95;1·33)	0·86 (0·79;0·94)	1·02 (0·90;1·16)	1·07 (0·93;1·22)	1·13 (0·95;1·33)
High	0·39 (0·22;0·71)	0·68 (0·51;0·89)	0·66 (0·47;0·91)	0·82 (0·72;0·92)	0·38 (0·23;0·63)	0·73 (0·48;1·10)	0·63 (0·51;0·77)	0·90 (0·68;1·20)
	I^2 = 85% p=0·01	I^2 = 86% p=0·008	I^2 = 86% p=0·007	I^2 = 90% p=0·002	I^2 =89% p=0·002	I^2 = 59% p=0·12	I^2 = 94% p<0·0001	I^2 = 42% p=0·19
Age								
15-19 yrs	0·69 (0·60;0·79)		0·95 (0·84;1·08)		0·67 (0·56;0·80)		0·91 (0·78;1·07)	
20-24 yrs		0·84 (0·75;0·94)		0·96 (0·83;1·10)		0·86 (0·77;0·95)		0·97 (0·86;1·10)
25-29 yrs		0·88 (0·75;1·02)		1·04 (0·89;1·21)		0·91 (0·80;1·04)		1·08 (0·95;1·23)
30-39 yrs		1·04 (0·92;1·18)		1·06 (0·93;1·21)		1·08 (0·96;1·20)		1·11 (0·99;1·24)
		I^2 = 70% p=0·04		I^2 = 0% p=0·55		I^2 = 78% p=0·01		I^2 = 20% p=0·29
Years since vaccination								
Year 1	0·84 (0·73;0·97)	0·93 (0·85;1·02)	1·00 (0·96;1·04)	1·01 (0·94;1·08)	0·82 (0·68;0·99)	0·96 (0·88;1·03)	0·96 (0·88;1·05)	1·03 (0·97;1·10)
Year 2	0·67 (0·56;0·80)	0·88 (0·77;1·01)	0·97 (0·85;1·12)	0·97 (0·84;1·11)	0·62 (0·45;0·84)	0·94 (0·85;1·05)	0·86 (0·68;1·09)	1·04 (0·94;1·16)

	Baandrup et al.				Sandø et al.			
	Females		Males		Females		Males	
	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs
Year 3	0·73	0·91	1·02	1·07	0·73	0·91	1·02	1·07
	(0·62;0·86)	(0·74;1·12)	(0·82;1·27)	(0·83;1·37)	(0·62;0·86)	(0·74;1·12)	(0·82;1·27)	(0·83;1·37)
Year 4	0·59	0·80	0·93	1·01	0·59	0·80	0·93	1·01
	(0·48;0·71)	(0·65;1·00)	(0·72;1·19)	(0·78;1·32)	(0·48;0·71)	(0·65;1·00)	(0·72;1·19)	(0·78;1·32)
	I^2 = 68%	I^2 = 0%	I^2 = 0%	I^2 = 0%	I^2 = 56%	I^2 = 0%	I^2 = 0%	I^2 = 0%
	p=0·02	p=0·65	p=0·92	P=0·91	P=0·08	p=0·53	p=0·75	·p=0·99
Data source								
Population-based	0·81	0·88	1·02	0·96	0·78	0·97	0·94	1·07
	(0·52;1·26)	(0·74;1·05)	(0·80;1·30)	(0·80;1·15)	(0·44;1·38)	(0·96;0·99)	(0·61;1·45)	(1·04;1·11)
Health/Insurance-based	0·81	1·07	1·04	1·17	0·81	1·07	1·04	1·17
	(0·76;0·87)	(0·90;1·26)	(0·88;1·24)	(0·93;1·48)	(0·76;0·87)	(0·90;1·26)	(0·88;1·24)	(0·93;1·48)
Clinic-based	0·33	0·63	0·58	0·82	0·33	0·63	0·58	0·82
	(0·11;0·99)	(0·42;0·93)	(0·39;0·86)	(0·65;1·02)	(0·11;0·99)	(0·42;0·93)	(0·39;0·86)	(0·65;1·02)
	I^2 = 23%	I^2 = 69%	I^2 = 73%	I^2 = 58%	I^2 = 24%	I^2 = 65%	I^2 = 72%	I^2 = 67%
	p=0·27	p=0·04	p=0·03	P=0·09	p=0·27	p=0·06	p=0·03	p=0·05
Results presented in Figure 4								
High coverage								
< 20 yrs								
Year 1	0·60		0·85		0·59		0·82	
	(0·48;0·74)		(0·69;1·04)		(0·49;0·71)		(0·76;0·89)	
Year 2	0·30		0·56		0·31		0·52	
	(0·22;0·41)		(0·42;0·75)		(0·23;0·42)		(0·47;0·57)	
Year 3	0·12		0·36		0·12		0·36	
	(0·07;0·21)		(0·21;0·59)		(0·07;0·21)		(0·21;0·59)	
Year 4	0·07		0·38		0·07		0·38	
	(0·03;0·13)		(0·23;0·63)		(0·03;0·13)		(0·23;0·63)	
20-24 yrs								
Year 1		0·75		0·94		0·77		0·97
		(0·61;0·91)		(0·86;1·01)		(0·59;1·00)		(0·82;1·14)
Year 2		0·60		0·73		0·69		0·85
		(0·45;0·80)		(0·64;0·82)		(0·49;0·96)		(0·69;1·04)
Year 3		0·22		0·53		0·22		0·53
		(0·16;0·31)		(0·45;0·63)		(0·16;0·31)		(0·45;0·63)
Year 4		0·17		0·45		0·17		0·45
		(0·12;0·25)		(0·37;0·54)		(0·12;0·25)		(0·37;0·54)
25-29 yrs								
Year 1		0·74		0·87		0·78		0·96
		(0·60;0·90)		(0·80;0·95)		(0·56;1·10)		(0·78;1·18)
Year 2		0·62		0·73		0·76		0·94
		(0·53;0·71)		(0·56;0·96)		(0·52;1·13)		(0·74;1·20)
Year 3		0·42		0·73		0·42		0·73
		(0·30;0·57)		(0·62;0·86)		(0·30;0·57)		(0·62;0·86)
Year 4		0·34		0·64		0·34		0·64
		(0·23;0·50)		(0·53;0·76)		(0·23;0·50)		(0·53;0·76)

	Baandrup et al.				Sandø et al.			
	Females		Males		Females		Males	
	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs
30-39 yrs								
Year 1		0·85 (0·76;0·95)		0·85 (0·76;0·95)		0·91 (0·75;1·11)		0·92 (0·73;1·17)
Year 2		0·79 (0·58;1·08)		0·79 (0·60;1·04)		0·97 (0·86;1·09)		0·99 (0·79;1·24)
Year 3		1·28 (0·98;1·67)		0·83 (0·71;0·97)		1·28 (0·98;1·67)		0·83 (0·71;0·97)
Year 4		0·78 (0·56;1·09)		0·76 (0·65;0·90)		0·78 (0·56;1·09)		0·76 (0·65;0·90)

Figure S1. Changes in the incidence of high-grade cervical lesions between the pre and post-vaccination period among females aged 15-39 years old.



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